CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021028

CHEMISTRY REVIEW(S)

IND 41087

FEB - 3 1999

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA #: 21-028
CHEMISTRY REVIEW #: 1

DATE REVIEWED: 2-3-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
ORIGINAL	7-23-98	7-29-98
AMENDMENT	12-1-98	12-2-98
AMENDMENT	12-23-98	12-28-98

NAME & ADDRESS OF APPLICANT:

Novo Nordisk Pharmaceuticals, Inc
Suite 200
100 Overlook Center
Princeton NJ 08540

DRUG PRODUCT NAME

Proprietary:	Velosulin BR
Established:	buffered regular human insulin injection (rDNA origin)
Code Name/#:	
Chem.Type/Ther.Class:	3/S

ANDA Suitability Petition / DESI / Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: antihyperglycemic

DOSAGE FORM:	Injection
STRENGTHS:	100 U/mL
ROUTE OF ADMINISTRATION:	S.C. Injection
DISPENSED:	___ Rx _X_ OTC
SPECIAL PRODUCTS:	_X_ Yes ___ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

See "Human Insulin"

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
NDA 19-938	Human Insulin, (rDNA origin)	Novo Nordisk A/S	approved	N/a	N/a

RELATED DOCUMENTS:
NDA 19-450, Velosulin BR (semi-synthetic)
IND [redacted]

APPEARS THIS WAY ON ORIGINAL

NDA: 21-028

CONSULTS:
Microbiology (see review #2 dated 27-JAN-1999).

REMARKS:

This application represents a change in the source of drug substance for this "Pump" insulin from semi-synthetic human insulin to recombinant human insulin. This insulin is intended only for use in external pumps, and is labeled as such, however, the option of conventional dosing via a syringe is also included. Minor differences in the formulation of the proposed product compared to the currently approved version have been made, and the differences were studied in bioequivalence trials. Minor modifications to some of the drug product release specifications were made to account for these differences, and acceptable justification has been made in support of these changes. The amendment of 12-1-98 provided assurance that the manufacturing equipment and its location is the same as that for the current product approved under NDA 19-450.

CONCLUSIONS & RECOMMENDATIONS:

The sponsor has provided adequate CMC information to support the manufacture, packaging and labeling of Velosulin BR formulated using recombinant drug substance rather than the current product formulated using semi-synthetic drug substance. Adequate stability data derived from acceptable protocols has been provided to support the proposed 30-month expiration date for the proposed product. The labeling, provided in support of the recombinant product, mirrors the currently approved labeling for the semi-synthetic product, with the exception of references to "rDNA" vs. "semi-synthetic" origin for the drug substance. Therefore, the proposed labeling is acceptable. It should also be noted, however, that the two "products" will be on the market simultaneously with the same trade name, until the supply of the semi-synthetic product runs out. The manufacturing facility received an "acceptable" recommendation from the Office of Compliance. The CDER office of Microbiology has recommended that the application be approved on the basis of assurance of sterility.

This application is recommended for approval on the basis of CMC review. There are no deficiencies or "requests for information" to be forwarded to the sponsor pursuant to this review.

cc:
Org. NDA 21-028
HFD-510/Division File
HFD-510/Wberlin/SMoore
HFD-510/CSO

R/D Init by: SMoore

/S/ [redacted]
William K. Berlin, Review Chemist

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/S/ [redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021028

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA:	21-078	MAR 25 1999
Sponsor:	Novo Nordisk	
Drug:	Velosulin BR human buffered regular human insulin injection (recombinant DNA origin)	
Indication:	Diabetes	
Documents reviewed:	Volumes 1.1, 1.5-1.9	
Medical Reviewer:	Robert Misbin, M.D. (HFD-510)	
10-month User Fee date:	May 23, 1999	

Introduction

The sponsor has submitted two studies, a bioequivalence study (008) and a Phase 2 efficacy study (009), in support of the efficacy of Velosulin, a buffered human insulin (rDNA origin) given by continuous infusion from pumps, in the management of diabetes. Study 009 compared the test drug (insulin of recombinant DNA origin or "rDNA") to the standard buffered regular human insulin of semi-synthetic origin ("semi synthetic"). The drugs to be compared had the same chemical structure but were synthesized differently. Study 009 is the subject of this review.

009 Study Design

Study 009 was a single center, open-label, randomized crossover study in 20 male Caucasian type-1 diabetics experienced in using insulin pumps. Subjects were randomized to receive one of the following treatment sequences:

	Period 1 (4 weeks)	Period 2 (4 weeks)
Sequence 1 (n=10)	rDNA insulin	Semi synthetic insulin
Sequence 2 (n=10)	Semi synthetic insulin	rDNA insulin

The initial insulin dose was based on the subject's usual (pre-study) dose. Treatment periods were four weeks, with the first week of each period (washout) used to adjust the insulin dose to reach a "consistent" treatment regimen, presumably for adequate glycemic control. During treatment, patients could adjust their insulin doses to maintain glucose levels at adequate levels.

The primary objective of the study was to describe the efficacy and safety of rDNA insulin compared to semi synthetic insulin. The primary outcome variable per protocol was the average daily insulin dose measured the last three weeks of each treatment period. There were a number of secondary variables:

- Fructosamine levels at the end of each treatment period

- Mean daily glucose levels (fasting, pre-lunch, pre-dinner, and bedtime)
- Number of fingerstick glucose determinations greater than 400 mg/dl or less than 60 mg/dl in 3 weeks, counted separately
- Number of obstruction/leakages of infusion sets over the last three weeks of each treatment period

Per protocol, an ANOVA based on the 2x2 crossover model would be used to test the null hypothesis of no difference between treatments on the primary endpoint. The error term derived from the model would be used to construct a 95% confidence interval for the estimated treatment difference.

Sponsor's Results

Table 1 (Appendix) shows demographic characteristics of the study subjects. All twenty randomized subjects completed the study. There were significant ($p<.05$) pre-treatment imbalances between sequence groups for screening fructosamine, and Day 1 and 2 pre-lunch glucose levels (not shown in Table: sequence R/S, 197 mg/dl; sequence S/R, 121 mg/dl).

Mean insulin doses during treatment are shown in Table 2 (Appendix) for each patient. The analyses conducted by the sponsor normalized this endpoint by body weight in kilograms. The sponsor analyzed fructosamine as changes from screening to the end of the 4-week periods due to significant sequence group differences for the raw values.

The statistical model was:

Mean daily insulin dose = treatment sequence period patient(sequence).

Analysis results are shown in Table 3 below. The mean difference in daily insulin dose between the two treatments (semi synthetic minus rDNA) was -0.014 units/kg. The 95% confidence interval for the difference was (–0.042, 0.014) which overlaps the 'zero' difference.

Table 3: Between treatment comparison of mean daily insulin dose

	rDNA	Semi synthetic	Between treatment comparison		
	n=20	n=20	Diff	95% conf interval	p-value
Insulin dose (mg/kg)					
Mean (sd)	0.576 (0.145)	0.563 (0.156)	-0.014	(-0.042, 0.014)	.31

Secondary endpoint results are shown in Table 4. Pre-breakfast (fasting) glucose levels were significantly higher ($p=.035$) for rDNA compared to semi synthetic, whereas pre-lunch glucose levels were marginally lower ($p=.063$). There were significant sequence group differences for pre-lunch and pre-dinner glucose levels. According to the sponsor,

these significant sequence effects were not caused by carryover but represented a true difference between sequence groups.

Table 4: Between treatment comparisons of blood glucose and fructosamine

	rDNA	Semi synthetic	Between treatment comparison		
	n=20	n=20	Diff	95% conf interval	p-value
Blood glucose (mg/dl)					
Pre-breakfast mean (sd)	141.2 (28.7)	132.3 (31.3)	-8.9	(-17.1, -0.7)	.035
Pre-lunch mean (sd)	156.5 (38.6)	171.3 (61.2)	14.8	(-0.9, 30.5)	.063
Pre-dinner mean (sd)	140.2(41.5)	142.9 (32.5)	2.6	(-13.5, 18.8)	.74
Bedtime mean (sd)	170.8 (43.5)	175.7 (37.4)	4.9	(-10.7, 20.5)	.52
Fructosamine (umol/L)					
Mean change /screen (sd)	3.1 (29.5)	0.5 (27.4)	-2.6*	(-13.2, 8.0)	.61

* Sponsor's Table 8-2 shows incorrect beween-treatment mean differences for each sequence group. The incorrect means are small by a factor of 10.

Reviewer's Comments

The 95% confidence interval results suggest that insulin dose differences (semi synthetic minus rDNA) as large as -0.042 units/kg are consistent with the observed difference (-0.014 units/kg). The 95% confidence interval for the difference in unadjusted (not weight normalized) insulin dose (units), the protocol-defined endpoint, was (-3.5, 1.0).

Figures 1-6 show treatment-by-period plots for insulin dose and secondary endpoints fructosamine and glucose. Note that the direction of the treatment effect is reversed in the two periods in each plot. Overall, a higher rDNA dose (compared to semi synthetic) was associated with lower fructosamine and glucose levels, and visa versa.

There were significant ($p<.10$) carryover (sequence group) effects for pre-lunch glucose, pre-dinner glucose and fructosamine. The sponsor claims these significant effects were, in fact, true sequence group differences. In general, the null hypothesis of equal carryover can be rejected due to true carryover, treatment-by-period interaction or sequence group differences. These effects are confounded in the 2-by-2 crossover design. Here, the sponsor's assessment of causation (sequence differences) seems reasonable since there were significant differences at baseline between the groups on several variables. Furthermore, these differences were maintained during the treatment periods.

Conclusions

The randomization may not have been effective in allocating subjects to the sequence groups, perhaps due to subject selection bias. This deficiency, if true, would affect the validity of the statistical results. In summary, due to limitations in the trial design (no

blinding) and shortcomings in study conduct (randomization ineffective in allocating subjects to the sequence groups), these data do not provide convincing statistical evidence of the equal efficacy of rDNA and semi-synthetic insulin.

/S/ [redacted]

J. Todd Sahlroot, Ph.D.
Mathematical Statistician

Concur: Dr. Nevius /S/ [redacted] 3-25-95

cc: Arch NDA 21-028
HFD-510/SSobel, RMisbin
HFD-510/EGalliers, JRhee
HFD-715/Division file, ENevius, TSahlroot
Chron

This review contains 4 pages of text, 2 pages of Tables and 2 pages of Figures.

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Table 1: Summary of Patient Characteristics

	semi synthetic → rDNA	rDNA → semi synthetic
No. Treated	10	10
Age (yrs)		
Mean (SD)	35.3 (9.60)	37.3 (11.61)
Min - Max	24 – 55	25 - 52
Race (%)		
Caucasian	100.0	100.0
Weight (kg)		
Mean (SD)	82.5 (9.38)	87.8 (9.24)
Min - Max	72 – 103	75 - 102
Height (cm)		
Mean (SD)	176.1 (5.91)	178.6 (7.31)
Min - Max	169 – 186	168 - 191
BMI (kg/m^2)		
Mean (SD)	26.6 (2.39)	27.5 (1.26)
Min - Max	23 – 30	26 - 30
Fructosamine (μmol/L)		
Mean (SD)	331.0 (35.90)	373.5 (37.65)
Min - Max	259 – 365	333 - 450
Hemoglobin A_{1c} (%)		
Mean (SD)	7.4 (0.71)	7.9 (0.75)
Min - Max	5.8 - 8.2	6.7 - 8.9

Data from Sponsor's End-of-Text Table 1

Table 2: Average Daily Insulin Dose Over 3 Weeks

Sub. No.	Screening Wt. (kg)	Period 1 (Weeks 2-4) Bolus	Basal	Total (unit/kg)	Basal/ Total	Period 2 (Weeks 6-8) Bolus	Basal	Total (unit/kg)	Basal/ Total	Avg. Daily Total Insulin Per. 1-2
Semi synthetic – rDNA										
3	76.8									-0.006
4	71.8									-0.168
5	102.7									-0.005
6	84.1									0.002
11	95.0									0.098
12	77.5									-0.013
15	79.1									-0.021
16	76.8									0.017
19	79.5									-0.020
20	81.8									0.059
rDNA - Semi synthe										
1	85.0									0.018
2	74.7									-0.040
7	101.4									0.021
8	84.5									-0.011
9	97.7									0.099
10	100.0									0.031
13	87.7									0.021
14	84.1									0.105
17	76.4									-0.026
18	86.4									0.024

Data from Sponsor's End-of-text Table 4

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Fig. 1: Mean Insulin dose (units/kg) by treatment and period

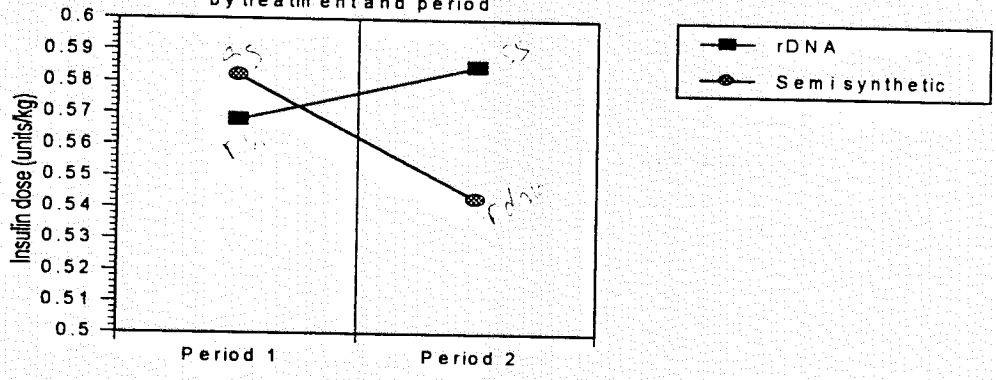

Fig. 2: Fructosamine levels by treatment and period

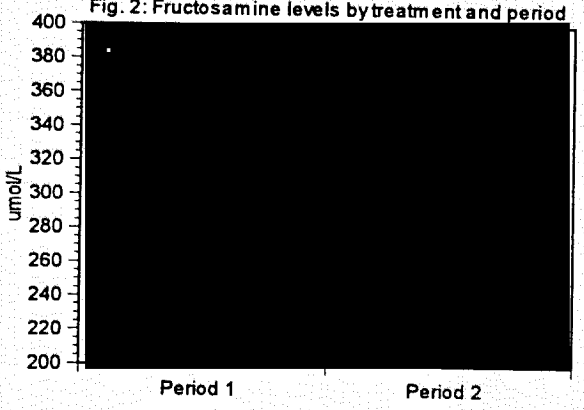

Fig. 3: Mean pre-breakfast glucose levels by treatment and period

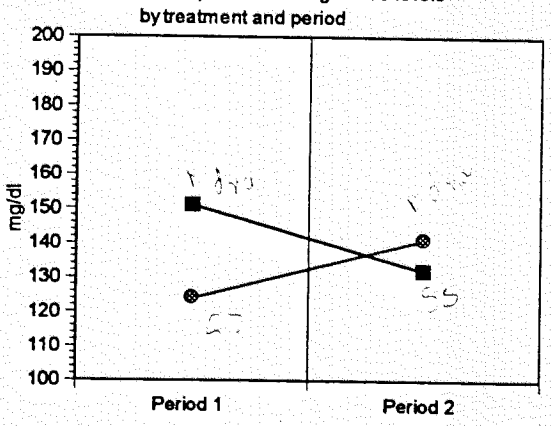

Fig. 4: Mean pre-lunch glucose levels by treatment and period

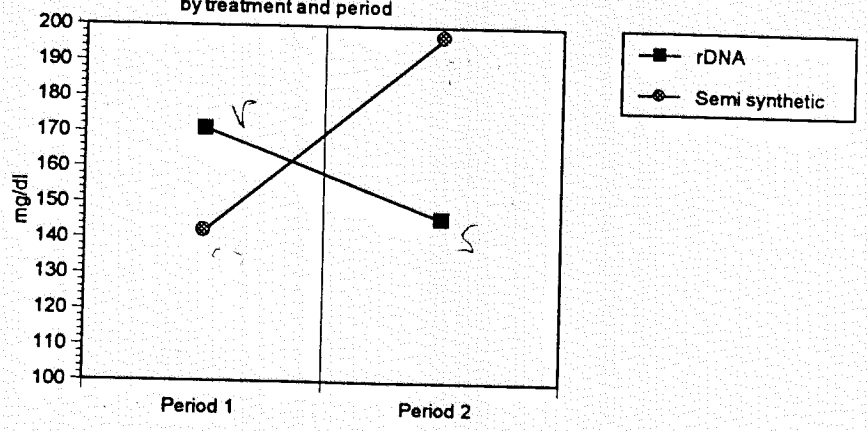

Fig. 5: Mean pre-dinner glucose levels by treatment and period

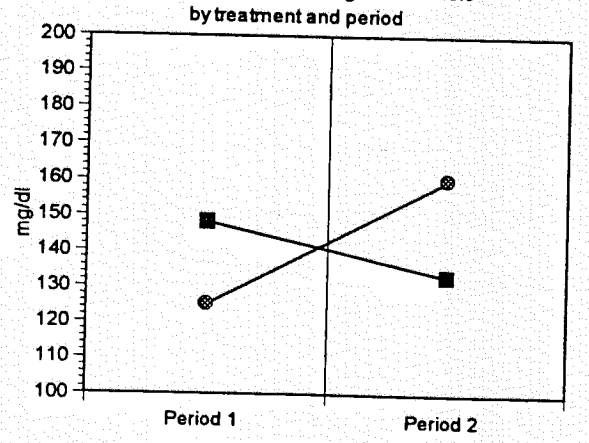

Fig. 6: Mean bedtime glucose levels by treatment and period